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Remimazolam; a role for anaesthesia/ sedation?

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I attach for your consideration a submission for Current Opinion in Anaesthesiology.

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We confirm that this paper has not been published in its current form or a substantially similar form (in print or electronically, including on a web site), that it has not been accepted for publication elsewhere, and that it is not under consideration by another publication.

Conflicts of interest

Professor Sneyd is an Advisory Board member and Consultant to Paion, the manufacturers of remimazolam.

Dr Rigby-Jones has no conflicts of interest.

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Title page

Title: Remimazolam; a role for anaesthesia/ sedation?

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Structured Abstract:

Purpose of review:

Anaesthesia and sedation are ubiquitous in contemporary medical practice. Developments in anaesthetic pharmacology are targeted on reducing physiological disturbance whilst maintaining or improving titrateability, recovery profile and patient experience. Remimazolam is a new short-acting benzodiazepine in the final stages of clinical development.

Recent findings:

Clinical experience with remimazolam comprises volunteer studies and a limited number of clinical investigations. In addition, laboratory investigations explore the implications of its “soft drug” pharmacology.

Summary:

Remimazolam provides effective procedural sedation with superior success rates and recovery profile when compared to midazolam. Comparisons with propofol are required. Preliminary studies suggest potential for using remimazolam as the hypnotic component of general anaesthesia. Definitive studies are awaited. As a benzodiazepine, remimazolam could be evaluated as an anticonvulsant and for intensive care sedation.

Keywords: Remimazolam, midazolam, propofol, sedation, anaesthesia

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Introduction

Remimazolam was developed to exploit in a benzodiazepine the esterase pharmacology successfully deployed in the opioid remifentanil, Figure 1. “Soft pharmacology”[1] offers precise control of drug effect by titration of boluses and infusion rate with rapid recovery when administration ceases. Current benzodiazepines cause minimal cardiorespiratory depression and the introduction of ester hydrolysis aims to combine several favourable characteristics in a single molecule i.e. the retention of benzodiazepine pharmacology with rapid degradation to an inactive metabolite.

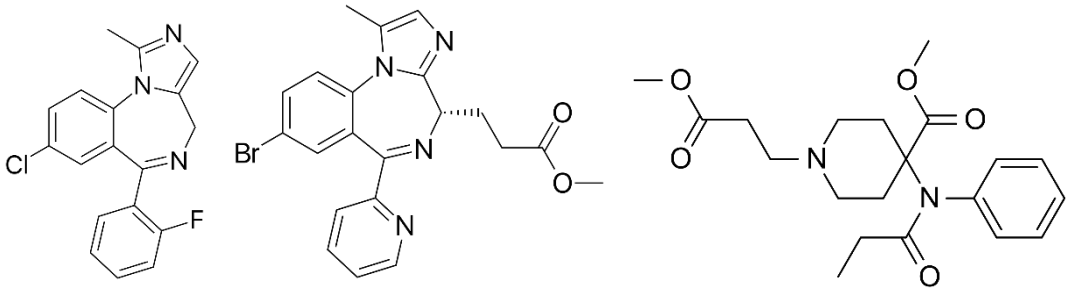

Figure 1. Midazolam, remimazolam and remifentanil. In remimazolam and remifentanil the introduction of an ester side group allows rapid hydrolysis[2] to inactive metabolites by carboxylesterase-1 (CES-1) mainly located in the liver .

Metabolism

Remimazolam is degraded to CNS7054 which appears to have negligible hypnotic activity. When human liver cells in a 3-D bioreactor were perfused with relevant concentrations of remimazolam to simulate prolonged anaesthesia or intensive care sedation, metabolism of remimazolam occurred at a stable rate over a five day period.[3] Gene expression of CES1 the enzyme that metabolises remimazolam was not altered during the study period.

Clinical pharmacology

In 1985 Belfast Professor John Dundee wrote: “Ideally one would like a water-soluble, non-irritant, rapidly-acting, smooth induction agent, with no antanalgesic action. Cardiovascular and respiratory depression should be minimal with normal dosage.” and “A slight delay in onset would not be a major obstacle, provided this is predictable…”.[4] Human studies of remimazolam have evaluated its safety and efficacy as an hypnotic and collected data to address the Dundee challenge.

Volunteer studies and early clinical trials confirm remimazolam to have typical benzodiazepine characteristics, Figure 2. Short infusions of remimazolam are hypnotic with dose related depth and duration of effect as measured by Bispectral Index, BIS or Modified Observer’s Assessment of Altertness/Sedation, MOAA/S scores. Heart rate and blood pressure were minimally perturbed. Pharmacokinetic and pharmacodynamic modelling of arterial remimazolam concentration and effect measures can be achieved with either mamillary or recirculatory models.[5-8]

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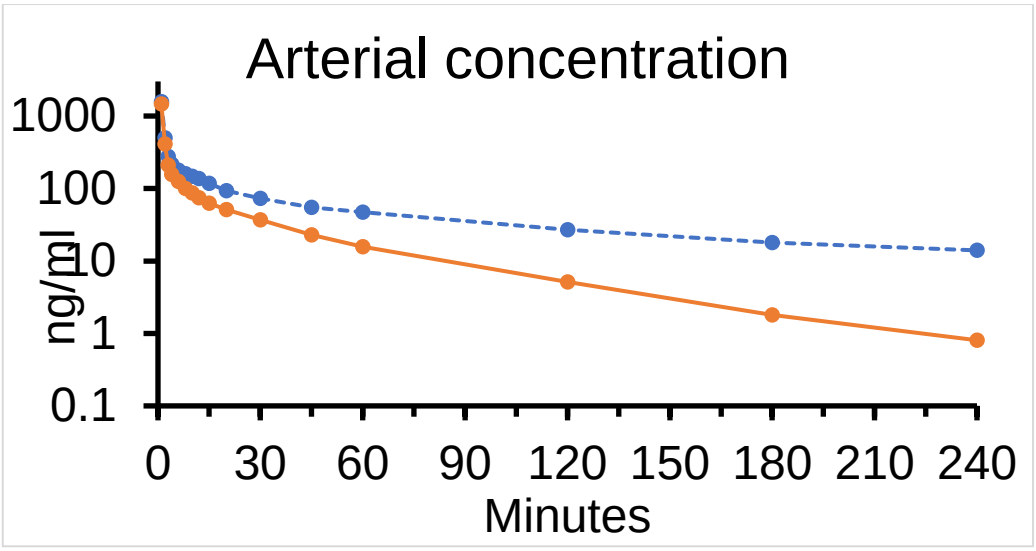
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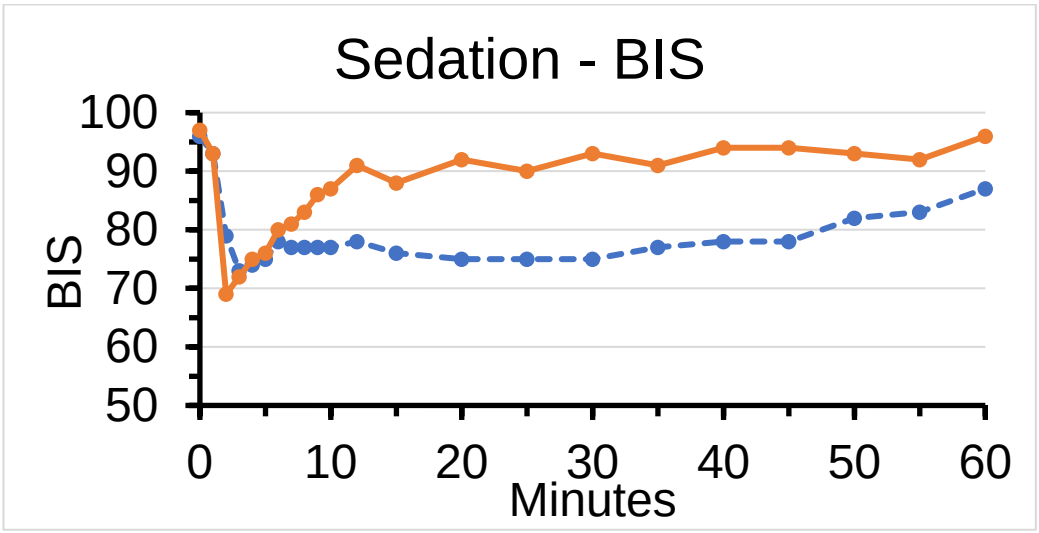
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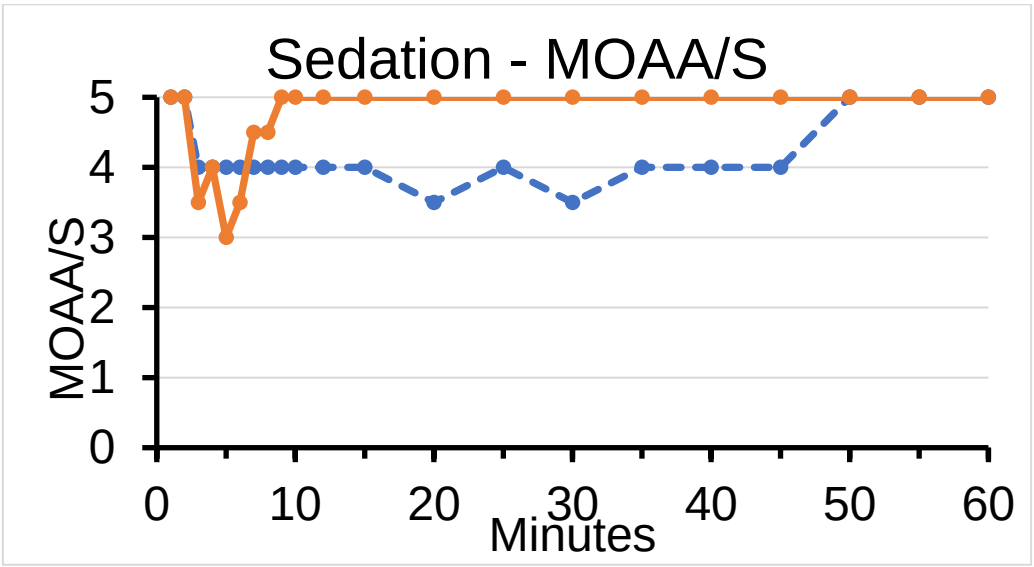
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Figure 2. A. Arterial concentrations (means) B. Bispectral Index, BIS (means) and (C) Modified Observer's Assessment of Alertness/Sedation Scale, MOAS/S (medians) in volunteers following a 1min infusion of remimazolam 0.075mg/kg (solid line) or midazolam 0.075mg/kg (dashed line). Original data replotted with permission from Anesthesia and Analgesia, Vol 115, Antonik,L.J. et al., A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics, Pages 274-283.[7] Copyright 2012, with permission from Elsevier.

Procedural sedation

Endoscopy, interventional cardiology and interventional radiology are frequently facilitated by patient sedation.[9] Guidance on Safe Sedation emphasises the importance of selecting an appropriate sedative agent as well as setting standards for equipment, staffing, competencies and audit.[10] Adjunct opioid may be given, typically as a single small dose administered before the sedative. Benzodiazepines have the advantage of a specific antagonist, flumazenil. Although the safe administration of low-dose propofol sedation by well-trained nurse sedationists has been described for selected diagnostic endoscopy procedures[11] the practice remains controversial.[12] Further, serious and relatively frequent morbidity has recently been reported in a large series of Australian patients receiving anaesthetist administered propofol to facilitate endoscopy.[13] Nevertheless, procedural sedation with propofol remains popular with patients and proceduralists because of its brief action and clear headed recovery.

Clinical trials of procedural sedation using remimazolam (typically supplemented by an opioid) have explored whether this new drug can provide rapid onset sedation with prompt recovery whilst minimising respiratory depression, airway obstruction and blood pressure perturbation.

Colonoscopy

Diagnostic colonoscopy is a common procedure performed in specialist clinics as well as in hospitals. Efficient patient throughput with patient satisfaction is a high priority and propofol sedation, typically administered by medically qualified anaesthesiologists, is preferred over midazolam because of the rapid onset and offset of propofol's sedative effect.

A substantial increase in anaesthetist input to colonoscopy, typically to administer propofol, has been identified and challenged. In a database review of 4,623,218 outpatient colonoscopies the proportion with 'anesthesia assistance' increased from 16.7% to 58.1% between 2003 and 2018.[14] Conversely, a recent database review of 44,794 colonoscopies in sedated patients concluded that propofol sedation was associated with small improvements in procedural quality indicators.[15] An outstanding question is whether these marginal gains can be replicated without the need for an anaesthesiologist. Large trials of procedural sedation using remimazolam have involved non-anaesthesiologist sedationists.[16, 17]

In a Phase 3 study, 461 patients undergoing colonoscopy were randomized to one of three arms: (i) remimazolam 5mg with supplementary doses of 2.5mg, (ii) placebo (with midazolam rescue), or (iii) open label midazolam (dosed according to the US label).[17] All patients received fentanyl 50-75mcg before the sedative or placebo. The pre-specified primary outcome measure of successful colonoscopy without rescue medication was achieved for in 91.3%, 1.7%, and 25.2% of patients receiving remimazolam, placebo, and midazolam respectively. Patients receiving remimazolam experienced less hypotension and recovered sooner than those receiving midazolam. Comparisons with propofol are awaited.

Bronchoscopy¶

Whereas colonoscopy without sedation is poorly tolerated, bronchoscopy is often performed without sedation using only topical anaesthesia. UK guidance in 2013 suggested offering patients the

option of sedation with a recommendation for non-anaesthetists to use midazolam rather than propofol.[18] However, the use of propofol in this context has increased and a recent meta-analysis concluded "Propofol sedation is able to reduce recovery time and shows similar safety compared with midazolam sedation during bronchoscopy".[19] When remimazolam, midazolam and placebo were compared in 446 patients undergoing flexible bronchoscopy (similar design as for colonoscopy described above), procedural success was 80.6, 32.9 and 4.8% respectively. Remimazolam was administered as a 5mg bolus supplemented by 2.5mg top-ups. Times to recovery of alertness and restoration of neuropsychiatric function were shorter with remimazolam than with midazolam.[20]

Anaesthesia

The use of benzodiazepines to provide the hypnotic component of general anaesthesia has been reported intermittently since the 1960's. By 1982 a critical evaluation of available benzodiazepines as candidate anaesthetics identified diazepam, flunitrazepam and midazolam as offering induction within 1-2 minutes whilst commenting that great individual variation in induction doses and long acting residual effects were problematic.[17] The favourable pharmacokinetics and pharmacodynamics of remimazolam now offer an opportunity to revisit this indication.

Although clinical trials registries including clinicaltrials.gov list multiple clinical trials of remimazolam in general anaesthesia and several are described as completed, none have yet been reported in peer-reviewed publications. However, some data have been reported as conference abstracts.[21-24] The detailed outcomes of these investigations are awaited and data describing onset and recovery times as well as arterial blood pressure will be especially interesting. Can remimazolam deliver the haemodynamic stability reported in earlier accounts of benzodiazepine anaesthesia with a responsiveness close to that of propofol?

Flumazenil reversal

Unlike propofol, remimazolam sedation may be completely reversed by the benzodiazepine antagonist flumazenil. In a preliminary study, three volunteers were deliberately sedated to loss of consciousness with remimazolam 0.25mg/kg. Sedation was reversed within one minute by flumazenil 0.5mg without subsequent re-sedation.[25]

Currently, the use of flumazenil after midazolam sedation is considered a red flag event suggesting overdosing and by implication poor clinical practice. Routine flumazenil reversal is discouraged because of the possibility of re-sedation.[26]

The short duration of remimazolam effect suggests that a more liberal approach might be considered if supported by properly designed clinical investigations. To date the clinical studies of remimazolam have only used flumazenil reversal as part of the management of rare instances of slow recovery from sedation or anaesthesia. In such circumstances the benzodiazepine (remimazolam) has usually been accompanied by an opioid. Appropriately designed clinical studies could usefully explore whether planned incorporation of flumazenil into end of sedation/anaesthesia protocols could enhance patient recovery.

TCI and closed loop delivery

Target controlled infusion, TCI is in worldwide use for propofol anaesthesia and sedation except in the United States where it remains without regulatory approval. Where TCI is available it is generally preferred over manual control. TCI for remifentanil is also available although its advantages over manual infusion are less clear-cut. Arguably, TCI delivery of remifentanil is of marginal benefit.**[27]**

Ultra-short acting drugs (norepinephrine for example) are easily titrated by simple adjustment of infusion rate and not susceptible to accumulation and are not generally delivered by TCI. The pharmacokinetics and pharmacodynamics of remimazolam are intermediate between those of propofol and remifentanil and we may reasonably expect remimazolam TCI to be useful.[5, 6]

Simulations of remifentanil TCI suggest that it would achieve steady state after 10 minutes versus 60

minutes for remimazolam and longer for propofol.[6] The original pharmacokinetic model for remimazolam is recirculatory rather than mammillary and therefore not suitable for TCI using currently available equipment. However, development of a multi compartment mammillary PK/PD model including an effect site has been recently reported[5, 6] and we can expect to see remimazolam TCI developed in due course.

Closed-loop anaesthesia and sedation require an appropriate measure of hypnosis to provide feedback into the infusion controller. Bispectral Index, BIS and other EEG derivatives have been used in for this purpose however no closed-loop system has been successfully commercialised or licensed to date. Whereas the BIS algorithm has been optimised to provide an approximately linear and monotonic response to increasing doses of propofol or volatile anaesthetic agents its calibration against benzodiazepines is less clear. A small number of benzodiazepine sedated patients were included within the original BIS development[28] however its value for estimating hypnosis in patients receiving remimazolam is not as clear and straight forward as for propofol. Likewise, in volunteers receiving remimazolam, the Narcotrend Index "showed a relatively weak and discordant relationship to the Modified Observer's Assessment of Alertness and Sedation score".[5] In general the EEG effects of benzodiazepines are somewhat different from those of volatile agents. After remimazolam administration commences there is frontal beta-activation followed by delta waves, a pattern seen with other intravenous agents.[29]

Environmental impact

Concerns about the anaesthetic contribution to climate change are rightly escalating.[30] The inhalational anaesthetics, especially desflurane and nitrous oxide have unfavourable environmental profiles and their replacement by routine use of intravenous anaesthesia has been advocated. In this regard remimazolam may prove to be an alternative to propofol.

Onco-anaesthesia and neurotoxicity

The effects of anaesthetic drugs on cancer progression and recurrence are currently the subject of much research. Likewise, the possibility of neonatal neurotoxicity has generated concern. However, without clear evidence of harm in clinical practice anaesthetists have been advised to continue their current practice including inhalational anaesthesia for patients undergoing cancer surgery[31] and appropriate general anaesthesia for neonates when necessary.[32] Given this background of uncertainty the benzodiazepine pharmacology of remimazolam gives no reason for concern whilst the relevant basic science and clinical research are executed.

Avoidance of hypotension

A recent review of the relationship between arterial blood pressure and organ dysfunction identified that 10 minutes or more with mean arterial pressure below 80 mm Hg may represent a threshold for organ injury by perioperative hypotension,[33] although further understanding the consequences of its different causes remains a priority.[34] Minimising hypotension therefore becomes a goal for clinicians and developers of new anaesthetics alike and has already been claimed for alfaxalone formulated in cyclodextrin.[35] Pioneers of benzodiazepine anaesthesia noted only modest changes in arterial blood pressure during induction[36, 37] and the potential for decreasing perioperative hypotension and its harms comprises one of the techniques greatest potential advantages., Whether remimazolam as an hypnotic has haemodynamic advantages over volatile anaesthetics or propofol requires careful evaluation, preliminary data are encouraging.[21-23, 38]

Conclusion

Clinical investigations of remimazolam suggest that it is a safe and efficacious sedative. As was the case when remifentanil was introduced, distinctive pharmacology may lead to novel applications which in turn must be carefully evaluated.

Key points:

- Remimazolam is a novel benzodiazepine ester susceptible to hydrolysis by carboxylesterase-1 (CES-1) mainly located in the liver.
- In randomised controlled trials of procedural sedation remimazolam shows quicker onset and offset of hypnotic effect than midazolam.
- Preliminary reports suggest remimazolam may be used as the hypnotic opponent of a total intravenous anaesthesia, TIVA technique.
- Remimazolam exhibits the cardiorespiratory stability typical of benzodiazepines and its effects can be fully reversed by flumazenil.
- The pharmacokinetics and pharmacodynamics of remimazolam can be described using standard 3-compartment effect site models and the drug may be suitable for target controlled infusion, TCI.

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None

Conflicts of interest

Professor Sneyd is an Advisory Board member and Consultant to Paion. For the remaining authors none are declared.

Reference section: references should be in numerical sequence (Vancouver style) and should include the first three authors or all authors if there are four or fewer. References from within the review

period should be annotated and bulleted as detailed below.

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An example of bulleted and annotated reference section is shown below.

One bullet annotations: still to be done

* Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjo¨ gren's syndrome. Ann Rheum Dis 2007; 66:351–357.

This is the first clinical trial to demonstrate the efficacy of B-cell depletion in SjS.

This article highlights the importance of B cells in the pathogenesis of SjS.

Two bullet annotations:

** Lavie F, Miceli-Richard C, Ittah M, et al. Increase of B-cell activating factor of the TNF family (BAFF) after rituximab: insights into a new regulating system of BAFF production. Ann Rheum Dis 2007; 66:700–703.

This study describes the elevation in BAFF levels that occurs in serum of patients who have been treated with B-cell depleting agents. This observation may have important consequences, following treatment, in promoting the corruption of B-cell tolerance and leading to disease relapse.

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